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HONEY AS A VEHICLE FOR MEDICINAL PREPARATIONS *

HONEY has been used in the formulation of medicinals since ancient times, but comparatively little scientific information concerning its suitability as a vehicle for medicinal products is available. The object of this investigation, performed over a period of two years, was to obtain such information. Twenty-one different types of liquid medicinal preparations were studied to find out if honey may advantageously replace part or all of the glycerin and/or syrup usually used in these liquids. In such a study the problem of the stability of the active ingredient(s) of a preparation containing honey is of primary importance. Because sugar-containing products may be susceptible to deterioration by microbiological organisms, this problem too is very important. And, taste is increasingly a matter of concern in evaluating medicinals. Finally, if honey is useful as an ingredient of a medicinal product, its producer must be assured that he may obtain the same, essentially uniform, honey each time he purchases it, for which reason quality specifications must be established for honey suitable for use in medicinal preparations. All these problems were investigated in the course of this study.

Stability of Various Medicinal Formulations

General

One of the variables investigated in these experiments was the effect of variation of pH on the different honey-containing vehicles. Honey is naturally acid in reaction, having a pH of approximately 3.7. When its pH is raised, two deleterious effects are observed: the honey becomes darker, and its aroma is markedly altered, becoming somewhat unpleasant; these effects are especially pronounced when the pH is above 7. The changes are largely attributable to degradation of the dextrose and levulose in honey.

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Another of these variables investigated was the effect of temperature on stability; data were obtained at room temperature, at 37°, and some at 50°. When stored at 50°, honey containing 10 per cent of added water (corresponding to the concentration of water in some of the vehicles) developed a brownish-black precipitate, from which behavior the unfavorable effect of elevated temperatures is apparent.

Honey suitable for use as a vehicle for medicinal products should be of the commercial variety designated as "heat-processed and filtered". With regard to clarity, some producers supply honey that may be used without further filtration; however, not all honeys described as having been filtered have acceptable clarity (though it should be noted that even the clearest honeys show the turbidity of colloidal solutions). The advantage of using honey that requires no filtration becomes apparent when this cumbersome operation does have to be performed, for which a suitable filter aid (0.5 to 0.75 per cent of Celite Standard Super Cel is satisfactory) is required and the filtration must be performed under pressure (10 to 14 lbs. per sq. in.). When adequately filtered honey is available for use in making solutions of water-soluble medicinal agents, the latter should be dissolved in the required amount of warm or hot water, the solution filtered and then mixed with the honey; this procedure suffices to give a clear solution.

Ferrous Sulfate Formulations

Several formulations, each containing the proportions of ferrous sulfate and citric acid specified in the formula for U. S. P. Ferrous Sulfate Syrup but differing in having as the vehicle a mixture of honey and water and in not containing peppermint spirit, were prepared. All these were completely stable, whether stored at 25° or 37°, as determined by periodic titrations with 0.1 *N* ceric sulfate during the period of observation of 11 months. All the solutions were very palatable; the following formula yields, in our opinion, a product with the most desirable viscosity.

Ferrous Sulfate	40	Gm.
Citric Acid, hydrous	2.1	Gm.
Water	210	Gm.
Honey *	1150	Gm.

* In order to know the exact composition of our preparations the ingredients were in most instances weighed; this formula yields approximately 1000 ml. of solution.

To prepare this solution, the ferrous sulfate and citric acid were dissolved in water with the aid of heat, the solution filtered, and mixed with the honey. The pH of the finished product is 2.6.

Sulfonamide Suspensions

Of the several formulations prepared and tested for stability, the one of the following composition seemed to us to have the most desirable physical characteristics. Settling of the suspended solids is slight and slow. Compared with three commercially available sulfonamide suspensions, it ranked first in the taste preference of a "panel" of 25 students. During 10 months of observation, the total sulfonamides content, as determined by titration with 0.1 *M* sodium nitrite, decreased only approximately 4 per cent.

Sulfadiazine (Calcomites®)	42	Gm.
Sulfamerazine (Calcomites®)	42	Gm.
Sulfamethazine (Calcomites®)	42	Gm.
Sodium Citrate	6.7	Gm.
Acacia	6.7	Gm.
Methylparaben	0.5	Gm.
Propylparaben	0.11	Gm.
Alcohol	17	Gm.
Glycerin	170	Gm.
Honey	950	Gm.
Water, sufficient to make a total of	1350	Gm.*

The suspension was prepared as follows: (1) the acacia was wetted with water, the remainder of which was used to dissolve the sodium citrate; (2) the parabens were dissolved in alcohol; (3) the sulfonamides were mixed with the glycerin and honey; (4) to the suspension of sulfonamides was added the solution of parabens; (5) to the mixture obtained in (4) the acacia and sodium citrate solutions were added, alternately; (6) the product was passed through a colloid mill. The pH of the finished suspension is 5.9. In place of the parabens, 0.05 per cent (w/v) of sorbic acid may be used as the preservative.

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* This corresponds to about 1000 ml. of suspension, each 4 ml. of which contains about 0.5 Gm. of mixed sulfonamides.

Preparations for Cough

Honey has long been used, especially in Europe, as an ingredient of preparations intended for treatment of cough, for which purpose it is well suited. We prepared several formulations of ingredients employed in contemporary products, and found two to have desirable characteristics which gave no physical evidence of change on standing fourteen (14) months (attempts to develop satisfactory quantitative procedures for the principal ingredients were unsuccessful). The preparations were very palatable. Clinical use of the products indicated them to have good antitussive action, which showed no evidence of diminution on storage.

The following are the formulas of the two preparations:

Dihydrocodeinone Bitartrate	0.32	Gm.
Pyrilamine Maleate	2.4	Gm.
Potassium Guaiacolsulfonate	32	Gm.
Sodium Citrate	16	Gm.
Citric Acid	16	Gm.
Sorbic Acid	0.5	Gm.
Water	160	Gm.
Honey	1150	Gm.

The solid ingredients were dissolved in about 140 Gm. of water with the aid of gentle heat, the solution filtered and the filter washed with the remainder of the water, and the filtrate and washings mixed with the honey.

Codeine Sulfate	2.1	Gm.
Promethazine Hydrochloride	1.05	Gm.
Potassium Guaiacolsulfonate	8.4	Gm.
Sodium Citrate	37.5	Gm.
Citric Acid	12.5	Gm.
Ipecac Fluidextract	2.3	ml.
Chloroform	4.1	Gm.
Water	155	Gm.
Glycerin	190	Gm.
Honey	940	Gm.

The water solution of the solid ingredients was prepared as for the preceding preparation. This solution was added to a mixture of

the fiuidextract, glycerin and honey and, when it had cooled to room temperature, the chloroform was incorporated. Filtration of the product, under pressure, and using filter aid (see above, under *General*), was found to be desirable.

Terpin Hydrate Formulations

Several preparations containing terpin hydrate were made. A variant of N. F. Terpin Hydrate Elixir, in which honey replaces the syrup and part of the glycerin, was found to be highly palatable and to remain clear on standing. The formula for this is:

Terpin Hydrate	16.9 Gm.
Sweet Orange Peel Tincture	20 ml.
Alcohol	425 ml.
Honey	400 ml.
Glycerin	200 ml.
Water, sufficient to make	1000 ml.

This elixir was made in the same manner as the N. F. elixir. After standing for several weeks a fine gelatinous precipitate formed but after removing this by filtration the product remained clear indefinitely.

Barbiturate Preparations

Several elixirs containing phenobarbital or pentobarbital in vehicles employing honey were prepared. While a few of the solutions remained fairly stable for six months, in our judgment none offered any advantage over the respective official preparations.

Vitamin Formulations

The stability of thiamine hydrochloride, riboflavin (as sodium riboflavin-5′-phosphate), cyanocobalamin, and ascorbic acid, separately, was studied in a vehicle of honey containing 10 per cent by volume of added water, at pH values ranging from 3.5 to 7.4, at room temperature and 37°, and in clear and brown bottles. Only riboflavin was acceptably stable, when stored in brown bottles, in the entire pH range, and at either temperature; decomposition at 77 days was of the order of 2 to 5 per cent. When stored in clear bottles, 25 to 30 per

cent of the riboflavin was decomposed in 6 days. Thiamine hydrochloride underwent considerable decomposition, and cyanocobalamin deteriorated very rapidly. Ascorbic acid was less stable in honey than in simple syrup; some stabilization was effected by adding 0.05 per cent of tetrasodium ethylenediamine tetraacetate, but not to a sufficient degree. In a solution containing both thiamine and riboflavin, the latter had a stabilizing effect on the former and both vitamins deteriorated to an extent of 2 to 5 per cent in the 63-day period of observation. Other mixtures did not show desirable stability characteristics. For extemporaneous compounding of these vitamins, honey may be used as a vehicle, if the preparation is stored in a brown bottle, and if used within a period of about 10 days.

Aspirin Preparations

Various combinations of aspirin with honey and other liquids were investigated in an attempt to prepare at least a suspension of acceptable stability. The most stable product we were able to obtain showed about 5 per cent hydrolysis of aspirin in two days, and approximately 12 per cent in five days (the analytical procedure was based on measurement of the intensity of color produced with salicylic acid on addition of ferric ion, the observation being made at 525 millimicrons in a spectrophotometer). Its formula, which represents approximately 2 grains of aspirin per 5-ml. teaspoonful, is:

Aspirin	28.8	Gm.
Alcohol	40	ml.
Glycerin	200	ml.
Honey, sufficient to make	1000	ml.

The aspirin was triturated with the alcohol, this mixture added, with constant stirring, to the glycerin, and this mixed with the honey. The pH of the suspension is 3.6.

Other Preparations

Variants of several official products, in which honey was incorporated in the respective vehicles, were prepared, these being: Compound Glycerophosphates Elixir; Iron and Ammonium Acetate Elixir; Iron, Quinine and Strychnine Elixir; Compound Opium and

Glycyrrhiza Mixture; Pepsin and Rennin Elixir; Compound Pepsin Elixir. These preparations were either not as palatable or stable, or both, as the official products.

Preservation Against Microorganisms

Because honey diluted with water is subject to deterioration by microbiological growth, the investigation of the effects of various preservatives is obviously of importance in evaluating the utility of honey as a vehicle for medicinals. Solutions containing various proportions of honey and water were inoculated with different organisms, and the effect of sorbic acid (0.05 and 0.1 per cent), sodium benzoate (0.1 per cent), and a mixture of methylparaben (0.2 per cent) and propylparaben (0.05 per cent) was determined. Sorbic acid in 0.05 per cent (w/v) concentration prevented fungous growth and spoilage; in 0.1 per cent concentration precipitation of some of the sorbic acid occurred in solutions containing a high proportion of honey. Sorbic acid may be incorporated by first dissolving it in hot water, then mixing this solution with honey. Potassium sorbate, which is more soluble in water, may be used in place of sorbic acid. With sodium benzoate (0.1 per cent), growth was observed in some cases. The mixture of parabens was not consistent in preventing growth; in part this may have been due to separation from the solutions of some of the propylparaben, crystals of which were identified by their infrared absorption spectrum. These experiments indicated sorbic acid to be the most effective preservative, and it appears advisable to include it in any preparation containing honey and water.

Quality Specifications

While standards for honey are provided in the monograph for it in the *National Formulary,* these standards will not insure constancy of different lots of honey, which is essential if uniformity of different batches of a product in which honey is an ingredient is to be maintained. The following specifications are more restrictive, and provide for greater uniformity of honey intended for use in medicinals.

General Description

Honey is the nectar of floral exudations of plants gathered and stored in the comb by honey bees, *Apis mellifera* Linné (Fam.

Apidae). It must be heat-treated for 30 minutes at 140° F. to 160° F. (maximum) and free from foreign substances such as parts of insects, leaves, etc., but may contain pollen grains. When graded according to the United States Standards for Grades of Extracted Honey (18 F. R. 52.1391-52.1404), it must be classified as "U. S. Choice" or "U. S. Fancy".

Moisture Content

Not more than 18.6 per cent, by weight. This corresponds to a refractive index ($n_D 20°$) of not less than 1.4900, and a specific gravity (20°/20° C.) of not less than 1.4129.

Optical Rotation

Honey is levorotatory at 20° C.

Residue on Ignition

Not more than 0.40 per cent.

Artificial Honey

Introduce 10 ml. of a mixture of equal volumes of honey and water into a test tube and add 5 ml. ether. Shake gently and allow to stand until the ether layer is clear. Transfer 2 ml. of this clear ether solution to a small test tube and add a large drop of freshly prepared resorcinol solution (1 Gm. resorcinol in 100 ml. of hydrochloric acid of sp. gr. 1.18-1.19). A cherry-red color appearing within one minute indicates the presence of artificial honey. Yellow to salmon shades have no significance.

Acidity

A solution of 10 Gm. of honey in 50 ml. of water requires not more than 5.0 ml. of 0.1 N sodium hydroxide for neutralization, using phenolphthalein as indicator.

Color

Shall not be darker than Light Amber, when determined by use of the U. S. D. A. permanent glass color standards.

Floral Type

Many floral types of honey are available, including those designated as follows: Alfalfa, Basswood, Clover, Cotton, Eucalyptus, Florida Orange, Mesquite, Palmetto, Sage, Star Thistle, Tulip Poplar, and others. The choice of floral type should be left to the discretion of the manufacturer of the product in which honey is used (clover honey was used in most of the formulations reported in this paper). Regardless of the floral type selected, the honey should meet all of the requirements proposed.

Packaging and Storage

Honey should be stored in well-closed containers, and the temperature should not exceed 90° F. for a prolonged period. Honey that has granulated may be liquefied in its container by heating at a temperature not over 160° F. for 30 minutes, with occasional stirring.

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